

Remarks / Arguments

Claims 1-12 are pending in this application. Claims 1, 6-10 and 12 have been amended. No new matter has been added.

Applicants point out that in the Preliminary Amendment of December 21, 2001, the expression "as component A" was by error not deleted from the amended version of the first paragraph of claim 1. In the claim set presented herein that language has now been removed.

Restriction/election

As restriction group I was previously elected for further prosecution, the non-elected subject matter has been deleted from claims 1 and 6-8. Applicants reserve the right to pursue non-elected subject matter in one or more continuing applications.

Claim Rejections - 35 USC § 112

Claim 9 has been rejected under 35 USC §112, first paragraph, the examiner stating "the specification, while being enabling for MTP inhibitors recited in claim 1, does not reasonably provide enablement for other suitable MTP inhibitor". Deeper in his argument, the examiner states "The instant claims read on all 'MTP inhibitors', necessitating an exhaustive search for the embodiments suitable to practice the claimed invention."

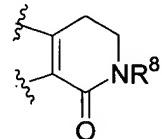
Applicants respond that the examiner has misinterpreted the claim language. Claim 9 recites "A pharmaceutical composition comprising a combination of an MTP inhibitor as component A and an HMG-CoA reductase inhibitor as component B according to Claim 1.....". The words "according to Claim 1" refer to and limit both "an MTP inhibitor as component A" and "an HMG-CoA reductase inhibitor as component B". The claim does not read on all MTP inhibitors as stated by the examiner, but only those recited in claim 1, which the examiner has stated are enabled. Applicants submit that claim 9, when read as a whole, is directed to "a

combination according to Claim 1". The rejection is therefore unfounded and its withdrawal is requested.

Claims 1-12 have been rejected under 35 USC §112, second paragraph, as being indefinite.

In particular, claim 1 has been rejected on grounds that the expression "R¹ and R², including the double bond connecting them..." renders the claim indefinite as to what moieties or substituents are encompassed by the claims.

Applicants respond that not every use of the word "including" renders a claim indefinite by permitting inclusion of unspecified other things. Each use of "including" needs to be considered in the context of the surrounding claim language. Here, the language is clear and unambiguous. It means that in formula (A1) of claim 1, R¹ and R², taken together with the double bond connecting them, form a phenyl or pyridyl ring or a ring of the formula



Accordingly, this rejection of claim 1 is deemed to be unfounded and its withdrawal is requested.

Claim 1 has also been rejected on grounds that the expression "R³ and R⁴, including the double bond connecting them, together form a phenyl ring or a 4- to 8-membered cycloalkene or oxocycloalkene radical" renders the claim indefinite as to what moieties or substituents are encompassed by the claims.

Applicants again respond that not every use of the word "including" renders a claim indefinite by permitting inclusion of unspecified other things. Each use of "including" needs to be considered in the context of the surrounding claim language. Here, the language is clear and unambiguous. It means that in formula (A1) of claim 1, R³ and R⁴, taken together with the double bond connecting them, form a phenyl ring or a 4- to 8-membered cycloalkene or

oxocycloalkene radical. Accordingly, this rejection of claim 1 is also unfounded and its withdrawal is requested.

Claim 1 has also been rejected on grounds that the expression "its part" in the paragraph of claim 1 describing the possible substituents on the rings created by the joining of R¹/R² and R³/R⁴ renders the claim indefinite as to which part is referred to. Applicant submits that, in accordance with standard English sentence construction, the expression "which for its part" refers to the preceding phrase "straight-chain or branched alkyl having up to 6 carbon atoms". Accordingly, this rejection of claim 1 is also unfounded and its withdrawal is requested.

Claim 2 has been rejected on grounds that the language "cardiovascular diseases are associated with metabolic diseases or deficits" renders the claim indefinite. The examiner states that the association between the cardiovascular disease and the metabolic diseases or deficits is not clear, and therefore, that it is not clear what cardiovascular diseases are encompassed by the claims.

Applicant submits that the association between cardiovascular diseases and metabolic diseases or deficits is in many cases well known and refer to Schwartz, S.M. and Bornfeldt, K.E., *Frontiers in Bioscience* 8, s1371-1383, September 1, 2003. This review article itself has been published *after* the filing date of the present application, but has been chosen for reasons of simplicity because it refers to a number of articles with publication dates *before* the filing date of the present application. As one example of the knowledge existing in the art, the abstract on page 1371 states:

"Risk factors for atherosclerosis, including diabetes, have been identified for many years, and, especially for lipids, we know a great deal about how these factors contribute to early lesion."

In this example, the association between the cardiovascular disease (atherosclerosis) and the metabolic disease (diabetes) in form of risk factors is disclosed and such association was well

known to the person skilled in the art at the time of filing of the present invention. Other examples could also be provided.

Regarding the examiner's statement that it is not clear what cardiovascular diseases are encompassed by the claims, applicants refer to the specification at page 51, where numerous cardiovascular diseases are recited. In view of the knowledge of the art and the extensive disclosure of the present specification, the rejection of claim 2 is deemed to be unfounded and its withdrawal is requested.

Claim 4 has been rejected on grounds that the expression "optionally associated with" renders the claim indefinite, the examiner stating "it is not clear how a secondary disorder being "optionally associated with" a disorder."

Applicants submit that claim 4 refers to "secondary hypercholesterolaemia and secondary hypertriglyceridaemia, which are optionally associated with apolipoprotein E polymorphism, obesity, chylomicronaemia and chylomicronaemia syndrome, renal insufficiency, chronic renal insufficiency, nephrotic syndrome, diabetes mellitus type II, and with hepatomas and plasmacytomas". In the context of this claim, the language "are optionally" means "may be", and applicants point out that such associations are known to the art. Applicants refer again to Schwartz, S.M. and Bornfeldt, K.E., *Frontiers in Bioscience* 8, s1371-1383, September 1, 2003, where item 3.2. on page 1372 states:

"Type 2 diabetes is associated with dyslipidemia, and dyslipidemia is considered the most significant cardiovascular risk factor in people with type 2 diabetes (10)."

Here again, the association between one disorder (type 2 diabetes) and another disorder (dyslipidemia, defined as hypertriglyceridaemia or hypercholesterolaemia in the specification as filed, page 52, line 27 *et seq.*) is disclosed and such association was well known to the person skilled in the art at the time of filing of the present invention. The rejection of claim 4 is therefore deemed to be unfounded and its withdrawal is requested.

Claim 9 has been rejected under 35 USC §112, second paragraph, for reciting the expression "if appropriate", and "one or more further suitable components". Claim 9 has now been amended to remove this language, overcoming the rejection.

Claim 12 has been rejected under 35 USC §112, second paragraph, for reciting the expression "if appropriate", and "with further components". Claim 12 has now been amended to remove this language, thus overcoming the rejection.

Claim 10 has been rejected under 35 USC §112, second paragraph, on grounds that it contains a trademark/trade name, namely ZD 4522.

Claim 10 has been amended to recite the expression "the calcium salt of (+)-(3R,5S)-bis-(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methane-sulphonylamo)-pyrimidin-5-yl)-3,5-dihydroxy-6 (E) heptenoic acid" instead of "ZD 4522". This amendment is supported by the specification as filed, page 20, line 28.

Claim Rejections - 35 USC §103

Claims 1-12 have been rejected under 35 USC §103 as being unpatentable over Muller et al. (US 5,684,014), and PDR 51st ed., 1997, page 770-774 (which deals with the HMG-CoA reductase inhibitor pravastatin).

The examiner's rationale for his *prima facie* determination of obviousness is basically that 1) Muller discloses the compounds presently claimed as useful for treating atherosclerosis, and 2) the PDR reference relating to pravastatin discloses that this material is a HMG-CoA reductase inhibitor which is useful in treating atherosclerosis due to hypercholesterolemia; therefore, as both materials are disclosed as being useful in treating cardiovascular diseases such as atherosclerosis individually, it would be obvious to use them in combination. This conclusion is legally deficient.

For a prima facie determination of obviousness to be proper, the art must suggest making the combination or the change to the prior art which the examiner asserts is obvious, and there must be an expectation of success if this is done. It is not sufficient that it may be obvious to try a combination or change to the prior art, and that the combination or change may be successful if tried.

In the present case, the art does not suggest using the combination of pravastatin and compounds of this application, and the art provides no reasonable expectation of success if the combination is made. At most, it might be obvious to try the combination. Those skilled in the art know that all pharmaceuticals have side effects, that sometimes combinations of pharmaceuticals can interact with each other or can operate in the body in a way which results in "adverse events", and that research has shown that certain pharmaceuticals should not be used in combination. Those skilled in the art do not subscribe to the notion that various pharmaceuticals which are disclosed for treatment of a given condition may necessarily be used in combination for treatment of that condition. Accordingly, it is deemed that the examiner's rejection on grounds of obviousness is unfounded, and its withdrawal is requested.

Respectfully submitted,



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